09/055,744

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| APPLICATION NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO. |
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EXAMINER

HM21/1208

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | 4 |

AIR MAIL

DATE MAILED: 12/08/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

## OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) 1-15 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-15 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☒ The specification is objected to by the Examiner.
☒ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of Reference Cited, PTO-892 2 pages
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

**--SEE OFFICE ACTION ON THE FOLLOWING PAGES--**

The Art Unit location of your application in the Patent and Trademark Office has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1648.

Applicant is encouraged to file an information disclosure statement including (1) a form PTO-1449, "Information Disclosure Citation" listing patents, publications and other information material to the instant application; (2) a concise explanation of the relevance of each listed item; (3) a copy of each listed item; and (4) a disclosure of related co-pending applications. See 37 C.F.R. §§ 1.97-1.98.

The following informality has been noted and requires correction in response to this Office Action. It is noted that Applicant's Figures are not numbered separately, i.e., Figure 3A, 3B, etc., in accordance with 37 CFR 1.84(i and j). **While submission of formal drawings can be held in abeyance until such time as allowable subject matter is determined, Applicant is required to amend the Brief Description of the Drawings, if necessary, in response to this Office Action to properly reflect the required corrections of the Drawings.**

The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. 1.67(a) identifying this application by its Serial Number and filing date is required. See M.P.E.P. 602.1 and 602.02. The oath or declaration is defective because:

1) it does not properly reference the specification as originally filed. The declaration indicates that the specification "is attached hereto" when, in fact, the declaration was filed subsequent to the filing of the original specification;

2) the signature of inventor Michel Klein is absent in the wrong place and the date of signing of inventor Michel H. Klein is missing.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825 for the reason(s) set forth on the attached Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

**APPLICANT IS GIVEN THREE MONTHS (the shortened statutory period of this Office Action) FROM THE DATE OF THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R. § 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 1-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards

as the invention. Claims 1 and 6 are vague and indefinite in the recitation "HIV-derived" since it is unclear to what extent and in what way the claimed protein is "derived" from HIV-1. Amendment of claims 1 and 6 to delete "derived" would obviate this rejection. Claim 2 is vague and indefinite in the recitation "HLA class II restricted T-helper epitopes" since it is unclear whether Applicant is actually referring to T cell stimulating epitopes of an HLA molecule or to HIV epitopes which are capable of interacting with an HLA molecule. Amendment of claim 2 to more particularly point out and define what is meant by "HLA class II restricted T-helper epitopes" would obviate this rejection. Claims 6-7 and 12 are vague and indefinite in the recitation "corresponding to" or similar language since it is unclear what is intended to be encompassed by the language "corresponding to." Amendment of claims 6-7 and 12 to delete "corresponding to" or similar language would obviate this rejection. Claim 12 is further vague and indefinite in the recitation "having an amino acid..." since it is unclear what the scope of "having" is and since the clause does not make sense in view of the language "amino acid". Amendment of claim 12 to recite "comprising" or "consisting of" in place of having as appropriate and to recite "an amino acid sequence of SEQ ID NO: 9..." would obviate this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant's claimed invention is directed to peptides of the rev protein of HIV and methods of use to induce CTL responses in a host. The claimed invention encompasses the use of the peptides in humans as vaccines for treating or preventing HIV infection (see specification, page 2, lines 9-24). However, it is well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies. The obstacles to therapy of HIV are well documented in the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation.

Further, it is well known in the art that individuals infected with HIV produce neutralizing antibodies and CTL responses to the virus, yet these antibodies and CTLs are not protective and do not prevent the infection from progressing to its lethal conclusion. Further, as taught by Fahey et al. (R), clinical trials using a variety of immunologically based therapies have not yielded successful results in the treatment and/or prevention of HIV infection (see Table 1). The failure of all immune-system-boosting

therapies for treating AIDS is further discussed by Fox (S). The teachings of Fahey et al. and Fox are further confirmed by Haynes et al. (T). Haynes et al. teach the major scientific obstacles blocking development of HIV vaccines (see page 40, first column, second full paragraph). Further, Haynes et al. teach that "Current animal models of either HIV or simian immunodeficiency virus (SIV) fall short of precisely mirroring human HIV infection" and that "lacking these models, researchers must turn towards human clinical trials to answer many of the difficult questions about HIV pathogenesis and HIV vaccine development" (see page 40, first column, third full paragraph). Thus, it is clear from the evidence of Fahey et al., Fox, and Haynes et al. that the ability to treat and/or prevent HIV infection is highly unpredictable and has met with very little success.

Applicants have not provided any convincing evidence that their claimed invention is indeed useful as a therapeutic or preventative for HIV infection and have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention with a reasonable expectation of success and without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

Further, Applicant's data is only directed to methods using MHC Class I HLA A2 molecules. Applicant has not set forth any evidence that the claimed methods could be used with MHC Class II molecules such as DR, DP and DQ molecules. Class I and Class II molecules differ in their structures and immunological specificities and it is unclear from the evidence of the specification that the two types of molecules can be used interchangeably in the claimed methods using the claimed peptides. Further, MHC restriction and regulation of the immune system may well limit the use of T helper molecules to a particular haplotype

for a particular individual, analogous to tissue typing for transplantation antigens. In other words it is unclear that the claimed method utilizing a DR7 molecule would satisfactorily stimulate a CTL response in a DR4 individual. Stimulating specific T cell responses to a particular epitope is unpredictable. This unpredictability is magnified when one attempts to modify the epitope in any way such as suggested in claim 12. In the absence of sufficient teachings or working examples for stimulating HIV specific CTL responses, one skilled in the art would not be able to make and use the claimed peptides and methods with a reasonable expectation of success and without undue experimentation.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> **A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**
>
> **Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligations under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-15 are rejected under 35 U.S.C. § 103 as being unpatentable over Blasevic et al., *AIDS Res. Hum. Retrovir.* 11(11):1335-1342, 1995 (Blasevic I, (U)) in view of Blasevic et al., *J. Acquired Immune Deficiency Syndromes* 6:881-890, 1993 (Blasevic II, (V)) and Schonbach et al., *Virology* 226:102-112, 1996 (W). Blasevic I discloses helper and cytotoxic T cell responses to synthetic peptides of HIV rev (see Abstract). Further, Blasevic et al. use synthetic peptides from the carboxyl terminal region of rev (see Table 1) and disclose that this region contains an HLA binding region (see Fig. 4). Thus, Blasevic I establishes that those of ordinary skill in the art recognized the importance and usefulness of identifying T cell epitopes within HIV rev. Blasevic I does not specifically disclose using palmitoyl or cholesterol to enhance immune responses.

Blasevic et al. II discloses T cell epitopes of another HIV regulatory gene, tat, and discloses epitopes recognized in association with MHC Class II molecules, particularly DR-2 (see Abstract). Schonbach et al. disclose the identification of T cell epitopes of HTLV-I, another T cell lymphotropic lentivirus. In particular, Schonbach discloses the use of synthetic peptides in combination with palmitoyl to produce lipopeptides (see Abstract).

The level of ordinary skill in the HIV vaccine art is exceptionally high and, absent convincing objective evidence to the contrary, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to identify T cell epitopes of the HIV rev protein according to the methods of Blasevic I and to use these peptides to stimulate T cell responses according to the methods of Blasevic I and Blasevic II and, further, to use the peptides as lipopeptides in accordance with the methods of Schonbach et al. for the expected benefit of obtaining improved immunotherapeutics for treating HIV infection. One of ordinary skill in the art would have been motivated by the

long felt need for improved therapies for HIV as evidenced by the evidence of Blasevic I and II and would have had a reasonable expectation of success since Schonbach et al. established that lipopeptides using palmitoyl were suitable for inducing CTL responses.

No claim is allowed.

Papers relating to this application may be submitted to Group 1600 by facsimile transmission. The Fax number is (703) 308-4242. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Robert D. Budens at (703) 308-2960. The Examiner can normally be reached Monday-Thursday from 6:30 AM-4:00 PM, (EST). The Examiner can also be reached on alternate Fridays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Chris Eisenschenk, can be reached at (703) 308-0452.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at (703) 308-0196.

Robert D. Budens
Primary Examiner
Art Unit 1648

rdb
December 6, 1998